

5 WHAT IS CLAIMED IS:

1. A method for determining whether a test compound is a candidate SKN-1-mediated oxidative stress response-activating compound, comprising:

(a) providing a first nematode capable of expressing a SKN-1 polypeptide and containing at least one transgene comprising:

(i) an oxidative stress resistance gene promoter operably linked to

(ii) a reporter gene; and

(b) contacting the first nematode with the test compound; and

(c) determining whether expression of the transgene is increased, wherein an increase in expression of the transgene indicates that the test compound is a candidate SKN-1-mediated oxidative stress response-activating compound.

2. The method of claim 1, further comprising determining whether the candidate compound is an inhibitor of GSK-3.

3. A method for determining whether a test compound is a candidate SKN-1-mediated oxidative stress response-inhibiting compound, comprising:

(a) providing a first nematode capable of expressing a SKN-1 polypeptide and containing at least one transgene comprising:

(i) an oxidative stress resistance gene promoter operably linked to

(ii) a reporter gene;

(b) contacting the first nematode with the test compound;

(c) before, during, or after step (b), subjecting the nematode to conditions that activate the SKN-1-mediated oxidative stress response in the absence of the test compound; and

(d) determining whether expression of the transgene is decreased or unchanged, wherein decreased or unchanged expression of the transgene

5 indicates that the test compound is a candidate SKN-1-mediated oxidative stress response-inhibiting compound.

4. The method of claim 3, further comprising determining whether the candidate compound is an inhibitor of SKN-1.

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5. A method for determining whether a test compound is a candidate SKN-1-mediated oxidative stress response-activating compound, comprising:

(a) providing a first nematode containing a transgene encoding a SKN-1 fusion protein, wherein the transgene comprises:

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(i) a SKN-1 DNA operably linked to

(ii) a reporter gene;

(b) contacting the first nematode with the test compound; and

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(c) determining whether the SKN-1 fusion protein accumulates in nuclei in the first nematode, wherein increased accumulation indicates that the test compound is a candidate SKN-1-mediated oxidative stress response-activating compound.

6. The method of claim 5, further comprising determining whether the candidate compound is an inhibitor of GSK-3.

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7. A method for determining whether a test compound is a candidate SKN-1-mediated oxidative stress response-inhibiting compound, comprising:

(a) providing a first nematode containing a transgene encoding a SKN-1 fusion protein, wherein the transgene comprises:

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(i) a SKN-1 DNA operably linked to

(ii) a reporter gene;

(b) contacting the first nematode with the test compound;

(c) before or during step (b), subjecting the first nematode to conditions that activate the SKN-1-mediated oxidative stress response in the absence of the test compound; and

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5 (d) determining whether the SKN-1 fusion protein accumulates in nuclei in the first nematode, wherein decreased or unchanged accumulation of the transgene indicates that the test compound is a candidate SKN-1-mediated oxidative stress response-inhibiting compound.

10 8. The method of claim 7, further comprising determining whether the candidate compound is an inhibitor of SKN-1.

9. The method of claim 1 or 5, further comprising the step of:

15 (d) providing a second nematode, not contacted with the candidate compound to determine whether the candidate compound increases oxidative stress resistance in the first nematode, relative to the oxidative stress resistance of the second nematode, wherein a candidate compound that increases oxidative stress resistance in the first nematode relative to the second nematode is an oxidative stress response-activating agent.

20 10. The method of claim 3 or 7, further comprising the step of:

25 (e) providing a second nematode not contacted with the candidate compound to determine whether the candidate compound decreases oxidative stress resistance in the first nematode, relative to the oxidative stress resistance of the second nematode, wherein a candidate compound that decreases oxidative stress resistance in the first nematode relative to the second nematode is an oxidative stress response-inhibiting agent.

30 11. The method of claim 1 or 3, wherein the promoter is a promoter of a gene encoding a protein selected from the group consisting of: γ -glutamine cysteine synthase heavy chain, glutathione synthetase, NADH quinone oxidoreductase, superoxide dismutase, catalase, and glutathione S-transferase.

35 12. The method of claim 1, 3, 5, or 7, wherein the reporter gene is a gene encoding a protein selected from the group consisting of: green fluorescent protein, chloramphenicol acetyl transferase, β glucuronidase, and luciferase.

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13. The method of claim 1 or 3, wherein the nematode in step (a) is *Caenorhabditis elegans*.

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14. The method of claim 5 or 7, wherein the nematode in step (a) is *Caenorhabditis elegans*.

15. A compound capable of activating a SKN-1-mediated oxidative stress response isolated by the method of claim 1 or 5.

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16. A compound capable of inhibiting a SKN-1-mediated oxidative stress response isolated by the method of claim 3 or 7.

17. An oxidative stress response-activating agent isolated by the method of claim 9.

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18. An oxidative stress response-inhibiting agent isolated by the method of claim 10.

19. The method of claim 1, further comprising the steps of:

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(c) providing a nematode not capable of expressing a SKN-1 polypeptide and containing at least one transgene comprising:

(i) an oxidative stress resistance gene promoter operably linked

to

(ii) a reporter gene; and

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(d) contacting the nematode with the test compound, wherein no increase in expression of the transgene following step (d) indicates that the candidate compound is an oxidative stress response-activating agent.

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20. A method for determining whether a test compound is a candidate compound capable of inhibiting a SKN-1-mediated oxidative stress response, comprising:

5 (a) contacting a SKN-1 polypeptide or SKN-1 DNA with a test compound; and

(b) detecting interaction of the test compound with the SKN-1 polypeptide or SKN-1 DNA, wherein an interaction indicates that the test compound is a candidate compound capable of inhibiting a SKN-1-mediated oxidative stress response.

21. A method for determining whether a test compound is a candidate compound capable of activating a SKN-1-mediated oxidative stress response, the method comprising:

15 (a) contacting a GSK-3 polypeptide, or fragment thereof, or a GSK-3 DNA with a test compound; and

(b) detecting the interaction of the test compound with the GSK-3 polypeptide, or fragment thereof, or GSK-3 DNA, wherein an interaction indicates that the test compound is a candidate compound capable of activating a SKN-1-mediated oxidative stress response.

22. The method of claim 21, wherein the fragment of GSK-3 comprises a SKN-1 binding fragment.

23. A method of determining whether a test compound is a candidate compound capable of activating a SKN-1-mediated oxidative stress response, the method comprising:

(a) providing a GSK-3 polypeptide, or fragment thereof, and a SKN-1 polypeptide, or fragment thereof;

30 (b) contacting the polypeptides or fragments thereof with a test compound; and

(c) detecting the interaction of the GSK-3 polypeptide, or fragment thereof, and the SKN-1 polypeptide, or fragment thereof, wherein a decrease in interaction indicates that the test compound is a candidate compound capable of activating a SKN-1-mediated oxidative stress response.

5 24. The method of claim 23, wherein the GSK-3 fragment comprises a SKN-1 binding fragment.

 25. The method of claim 23, wherein the SKN-1 fragment comprises an amino acid sequence comprising SEQ ID NO:1.

10 26. A method for determining whether a test compound is a candidate compound capable of inhibiting a SKN-1-mediated oxidative stress response, comprising:

 (a) providing a SKN-1 polypeptide or fragment thereof and an
15 oxidative stress resistance gene encoding γ -glutamine cysteine synthase heavy chain, glutathione synthetase, NADH quinone oxidoreductase, superoxide dismutase, catalase, or glutathione S-transferase, or SKN-1 polypeptide-binding fragments thereof;

 (b) contacting the SKN-1 polypeptide or fragment thereof and the
20 oxidative stress resistance gene or SKN-1 polypeptide-binding fragment thereof with a test compound; and

 (c) determining whether the SKN-1 polypeptide or fragment thereof
 and the oxidative stress resistance gene or SKN-1 polypeptide-binding
 fragment thereof interact in the presence of the test compound, wherein a
25 decrease in interaction indicates that the test compound is a candidate compound capable of inhibiting a SKN-1-mediated oxidative stress response.

 27. A fusion protein comprising a SKN-1 polypeptide fused to a heterologous amino acid sequence.

30 28. The fusion protein of claim 27, wherein the SKN-1 polypeptide comprises all or a biologically active fragment of SEQ ID NO:1.

 29. The fusion protein of claim 28, wherein the heterologous amino acid
35 sequence is a reporter protein.

5 30. A nucleic acid comprising a nucleotide sequence encoding the fusion protein of claim 27.

 31. A vector comprising the nucleic acid of claim 30.

10 32. A cell comprising the vector of claim 31.

 33. A transgenic nematode, one or more of whose cells comprise a transgene encoding a fusion protein comprising a SKN-1 polypeptide fused to a heterologous amino acid sequence, wherein the transgene is expressed in one or more cells of the
15 transgenic nematode.

 34. The transgenic nematode of claim 33, wherein the transgene comprises a *skn-1::gfp* transgene.

20 35. A transgenic nematode, one or more of whose cells comprise a transgene encoding a fusion protein comprising a GCS-1 polypeptide fused to a heterologous amino acid sequence, wherein the transgene is expressed in one or more cells of the transgenic nematode.

25 36. The transgenic nematode of claim 35, wherein the transgene comprises a *gcs-1::gfp* transgene.

 37. A transgenic nematode, one or more of whose cells comprise a transgene encoding a fusion protein comprising a GSK-3 polypeptide fused to a heterologous
30 amino acid sequence, wherein the transgene is expressed in one or more cells of the transgenic nematode.

 38. The transgenic nematode of claim 37, wherein the transgene comprises a *gsk-3::gfp* transgene.

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